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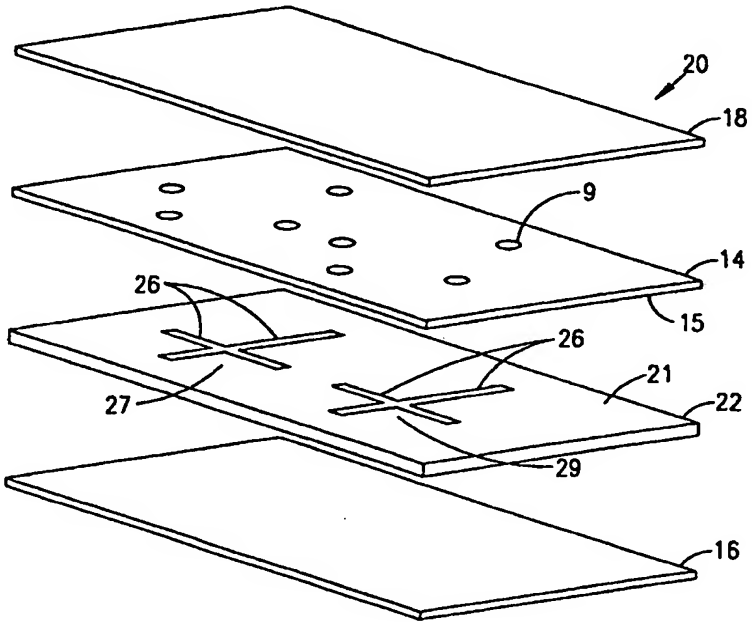
(54) Title: LAMINATE MICROSTRUCTURE DEVICE AND METHOD FOR MAKING SAME



(57) Abstract

A continuous form microstructure array device (20) is constructed as a flexible elongate film laminate containing microstructure arrays (26) arranged serially along the laminate. The laminate can be continuously drawn from a roll, passed through a processing and analysis device and rerolled or stacked for storage.

LAMINATE MICROSTRUCTURE DEVICE AND METHOD FOR MAKING SAME

BACKGROUND

This invention relates to methods and apparatus for high throughput sample analysis.

In a range of technology-based industries, including the chemical, bioscience, biomedical, and pharmaceutical industries, it has become increasingly desirable to develop capabilities for rapidly and reliably carrying out chemical and biochemical reactions in large numbers using small quantities of samples and reagents. Carrying out a massive screening program manually, for example, can be exceedingly time consuming and may be entirely impracticable where only a very small quantity of an important sample or component of interest is available, or where a component of a synthesis or analysis is very costly.

Developments in a variety of fields have resulted in an enormous increase in the numbers of targets and compounds that can be subjected to screening.

Rapid and widespread advances in the scientific understanding of critical cellular processes, for example, has led to rationally designed approaches in drug discovery. Molecular genetics and recombinant DNA technologies have made possible the isolation of many genes, and the proteins encoded by some of these show promise as targets for new drugs. Once a target is identified and the gene is cloned, the recombinant protein can be produced in a suitable expression system. Often receptors and enzymes exist in alternative forms, subtypes or isoforms, and using a cloned target focuses the primary screen on the subtype appropriate for the disease. Agonists or antagonists can be identified and their selectivity can then be tested against the other known subtypes. The availability of such cloned genes and corresponding expression systems require screening methods that are specific, sensitive, and capable of automated very high throughput.

Similarly, an emergence of methods for highly parallel chemical synthesis has increased the need for high throughput screening ("HTS"). Conventionally, preparation of synthetic analogs to the prototypic lead compound was the established method for drug discovery. Natural products were usually isolated from soil microbes and cultured under a wide variety of conditions. The spectrum of organisms employed by the pharmaceutical industry for isolation of natural products has now expanded from actinomycetes and fungi to include plants, marine organisms, and insects. More recently, the chemistry of creating combinatorial libraries has vastly increased the number of synthetic compounds available for testing. Thousands to tens or hundreds of thousands of small molecules can be rapidly and economically synthesized. *See,*

e.g., U.S. Patent No. 5,252,743 for a discussion of combinatorial chemistry. Thus, combinatorial libraries complement the large numbers of synthetic compounds available from the more traditional drug discovery programs based, in part, on identifying lead compounds through natural product screening.

Accordingly, considerable resources have been directed to developing methods for high-throughput chemical syntheses, screening, and analyses. A considerable art has emerged, in part from such efforts.

Competitive binding assays, originally developed for immunodiagnostic applications, continue to be commonly employed for quantitatively characterizing receptor-ligand interactions. Despite advances in the development of spectrophotometric- and fluorometric-based bioanalytical assays, radiolabeled ligands are still commonly employed in pharmaceutical HTS applications. Although non-isotopic markers promise to be environmentally cleaner, safer, less expensive, and generally easier to use than radioactive compounds, sensitivity limitations have prevented these new methods from becoming widespread. Another major disadvantage of the competition assay is the number of steps, most notably washing steps, required to run assays.

Scintillation proximity assays, discussed for example in U.S. Patent No. 4,271,139 and U.S. Patent No. 4,382,074, were developed as a means of circumventing the wash steps required in the above heterogeneous assays. The homogeneous assay technology, which requires no separation of bound from free ligand, is based on the coating of scintillant beads with an acceptor molecule such as, for example, the target receptor.

In another approach to avoiding the use of radioactive labels, especially useful in high-throughput assays, lanthanide chelates are used in time-resolved fluorometry. *See, e.g.*, U.S. Patent No. 5,637,509.

Automated laboratory workstations have contributed significantly to advances in pharmaceutical drug discovery and genomic science. *See, e.g.*, U.S. Patent No. 5,104,621 and U.S. Patent No. 5,356,525. Particularly, robotics technology has played a major role in providing practical means for carrying out HTS methods. *See, e.g.*, U.S. Patent No. 4,965,049.

Robotic-based high-throughput tools are now routinely used for screening libraries of compounds for the purpose of identifying lead molecules for their therapeutic potential. For example, a screening method for characterizing ligand binding to a given target employing a

variety of separation techniques is described in WO 97/01755, and a related method is described in U.S. Patent No. 5,585,277.

Highly parallel and automated methods for DNA synthesis and sequencing have also contributed significantly to the success of the human genome project, and a competitive industry has developed. Examples of automated DNA analysis and synthesis include, *e.g.*, U.S. Patent No. 5,455,008; U.S. Patent No. 5,589,330; U.S. Patent No. 5,599,695; U.S. Patent No. 5,631,734; and U.S. Patent No. 5,202,231.

Computerized data handling and analysis systems have also emerged with the commercial availability of high-throughput instrumentation for numerous life sciences research and development applications. Commercial software, including database and data management software, has become routine in order to efficiently handle the large amount of data being generated.

With the developments outlined above in molecular and cellular biology, combined with advancements in combinatorial chemistry, there has been a huge increase in the number of targets and compounds available for screening. In addition, many new human genes and their expressed proteins are being identified by the human genome project and will therefore greatly expand the pool of new targets for drug discovery. A great need exists for the development of more efficient ultrahigh throughput methods and instrumentation for pharmaceutical and genomic science screening applications.

Miniaturization of chemical analysis systems, employing semiconductor processing methods, including photolithography and other wafer fabrication techniques borrowed from the microelectronics industry, has attracted increasing attention and has progressed rapidly. The so-called "lab-on-a-chip" technology enables sample preparation and analysis to be carried out on-board microfluidic-based cassettes. Moving fluids through a network of interconnecting enclosed microchannels of capillary dimensions is possible using electrokinetic transport methods.

Applications of microfluidics technology embodied in the form of analytical devices has many attractive features for pharmaceutical high throughput screening. Advantages of miniaturization include greatly increased throughput and reduced costs, in addition to low consumption of both samples and reagents and system portability. Implementation of these developments in microfluidics and laboratory automation hold great promise for contributing to advancements in life sciences research and development.

first lamina having a first surface, providing a second lamina having a second surface, creating a plurality of openings in at least one of the first and second lamina, and apposing the first surface of the first lamina and the second surface of the second lamina to form a laminate structure, wherein each said opening is in fluid communication with one of said microstructures.

8. The method of claim 7, further comprising the step of apposing a surface of a flexible circuit laminate adjacent said first lamina, said flexible circuit laminate comprising a plurality of electrodes, wherein each said electrode is configured to contact an electroflow medium when such medium is supplied to said microstructure.

9. The method of Claim 7 wherein said forming step includes the step of embossing the first lamina to form said microstructures therein.

10. The method of Claim 9 wherein said forming step includes the step of curing the first lamina after the embossing step.

11. The method of Claim 7 further comprising the step of supplying the first lamina from a first roll and supplying the second lamina from a second roll in a continuous feed operation.

12. The method of Claim 11 further comprising the step of cutting the laminate structure to form a plurality of discrete devices each having a plurality of microstructures thereon.

13. A method for carrying out a microfluidic process, said method comprising the steps of providing a film laminate having a plurality of microstructures arranged therein, each said microstructure being configured to carry out at least one step in the microfluidic process, each said microstructure comprising a detection region, providing a detector capable of detecting a signal produced in the course of said step in said microfluidic process, causing relative movement between said film laminate and said detector to bring said detection region into the detection field of said detector.

14. A device for carrying out a microfluidic process, said device comprising

an elongate film laminate having a plurality of microstructures arranged therein, each said microstructure being configured to carry out at least one step in the microfluidic process, each said microstructure comprising a detection region,

a detector capable of detecting a signal produced in the course of said step in said microfluidic process,

means for moving said elongate film laminate or said detector in relation to each other to bring said detection region into the detection field of said detector.

15. A microstructure device for use with first and second contact probes extending from an electrode support structure in a predetermined pattern comprising a laminate structure having a first lamina of a plastic material, the first lamina having first and second spaced-apart parallel surfaces, the first lamina being provided with at least one microstructure extending in a direction parallel to the first and second parallel surfaces, the laminate structure having first and second spaced-apart wells adapted to receive a fluid and in fluid communication with the at least one microstructure, the laminate structure having a second lamina of a nonconductive material, electrical means at least partially carried by the second lamina for each of the first and second wells, each of the electrical means having an electrode portion in communication with the fluid of the respective well and a contact portion spaced apart from the respective well and not in fluid communication with the fluid of the respective well, the contact portions being arranged on the laminate structure in a pattern corresponding to the predetermined pattern of contact probes whereby the first and second contact probes can be brought into contact with the respective contact portions so as to provide a desired voltage potential to the fluid provided in the first and second wells.

16. The device of Claim 15 wherein each contact portion is accessible from the exterior of the laminate structure.

17. The device of Claim 16 wherein the second lamina has first and second spaced-apart parallel surfaces, each electrode portion being adjacent to the first surface of the second lamina and each contact portion being adjacent the second surface of the second lamina.

18. The device of Claim 17 wherein each of the first and second electrical means extends between the first and second surfaces of the second lamina so that each contact portion underlies the respective electrode portion.

19. The device of Claim 16 wherein each of the first and second electrical means includes a trace portion which electrically connects the contact portion to the electrode portion.

20. The device of Claim 19 wherein the electrode portion of each of the first and second electrical means is disposed at a bottom of a respective well.

21. The device of Claim 20 wherein the second lamina has first and second spaced-apart parallel surfaces, each electrode portion being adjacent to the first surface of the second lamina, each contact portion being adjacent to the second surface of the second lamina and each trace portion extending transversely between the first and second surfaces of the second lamina.

22. The device of Claim 16 wherein the laminate structure has first and second spaced-apart parallel surfaces, each of the first and second wells being accessible from the first surface and each of the contact portions of the first and second wells being accessible from the second surface.

23. The device of Claim 16 wherein the laminate structure has first and second spaced-apart parallel surfaces, each of the first and second wells and each of the contact portions of the first and second wells being accessible from the first surface.

24. The device of Claim 15 for use with first and second piercing contact probes wherein the second lamina is made of a material which permits the first and second piercing contact probes to penetrate the second lamina so that the first and second piercing contact probes electrically engage the contact portions of the first and second electrical means.

25. The device of Claim 16 wherein the laminate structure has a third lamina overlying the first and second wells for sealably enclosing the fluid in the first and second wells.

26. The device of Claim 15 for use with additional first and second contact probes wherein the first lamina is provided with an additional microstructure and the laminate structure has additional first and second spaced-apart wells in fluid communication with the additional microstructure, additional first and second electrical means at least partially carried by the second lamina for the additional first and second wells.

27. The device of Claim 15 for use with an additional first and second contact probes wherein the first lamina is provided with an additional microstructure, the laminate structure has additional first and second spaced-apart wells in fluid communication with the additional microstructure and the laminate structure has a third lamina of a nonconductive material disposed adjacent the second lamina, additional first and second electrical means at least partially carried by the third lamina for the additional first and second wells.

28. The device of Claim 27 wherein the second lamina overlies the first lamina and the third lamina overlies the second lamina.

29. The device of Claim 28 wherein the first and second wells and the additional first and second wells extend through the second lamina and the third lamina.

30. The device of Claim 15 wherein the first and second wells extend through the second lamina.

31. The device of Claim 30 wherein at least one of the electrode portions is annular in shape and extends around the respective well.

32. A microstructure device for use with first and second contact probes extending from an electrode support structure in a predetermined pattern comprising a laminate structure having an exterior and a first lamina of a plastic material, the first lamina having first and

second spaced-apart parallel surfaces, the first lamina being provided with first and second microstructures extending in a direction parallel to the first and second parallel surfaces, the laminate structure having first and second wells adapted to receive a fluid, the first well being in fluid communication with the first microstructure and the second well being in fluid communication with the second microstructure, the laminate structure having a second lamina and a third lamina each of a nonconductive material, first electrical means at least partially carried by the second lamina for the first well and second electrical means at least partially carried by the third lamina for the second well, each of the electrical means having an electrode portion in communication with the fluid of the respective well and a contact portion spaced apart from the respective well and not in communication with the fluid of the respective well, the contact portions being arranged on the laminate structure in a pattern corresponding to the predetermined pattern of contact probes whereby the first and contact probes can be brought into contact with the respective contact portions so as to provide a desired voltage potential to the fluid provided in the first and second wells.

33. The device of Claim 32 wherein the second lamina overlies the first lamina and the third lamina overlies the second lamina.

34. The device of Claim 33 wherein the first and second wells extend through the second lamina and the third lamina.

35. The device of Claim 34 wherein at least one of the electrode portions is annular in shape and extends around the respective well.

36. The device of Claim 33 wherein each of the first and second electrical means includes a trace portion which electrically connects the contact portion to the electrode portion, the trace portion of the second electrical means overlying the trace portion of the first electrical means and being electrically insulated from the trace portion of the first electrical means by the third lamina.

37. The device of Claim 32 wherein the laminate structure has a fourth lamina overlying the first and second wells for sealably enclosing the fluid in the first and second wells.

38. A microstructure device for use with first and second contact probes extending from an electrode support structure in a predetermined pattern comprising a laminate structure having a first lamina of a plastic material, the first lamina having first and second spaced-apart parallel surfaces and being provided with at least one microstructure extending in a direction parallel to the first and second parallel surfaces, the laminate structure having a second lamina of a nonconductive material, the second lamina having first and second spaced-apart surfaces and being provided with a plurality of spaced-apart bores extending through its first and second parallel surfaces for forming at least a portion of a plurality of wells adapted to receive a fluid and in fluid communication with the at least one microstructure, electrical means carried by the laminate structure for each of the plurality of wells, each of the electrical means having an electrode portion in communication with the fluid of the respective well and a contact portion spaced apart from the respective well and not in fluid communication with the fluid of the respective well, the contact portions being arranged on the laminate structure in a pattern corresponding to the predetermined pattern of contact probes whereby the first and second contact probes can be brought into contact with the contact portions so as to provide a desired voltage potential to the fluid provided in the plurality of second wells.

39. The device of Claim 33 wherein the first lamina is provided with an additional such microstructure and the second lamina is provided with an additional plurality of such spaced-apart bores for forming at least a portion of an additional plurality of wells in fluid communication with the additional microstructure, additional such electrical means carried by the laminate structure for each of the additional plurality of wells, the additional electrical means overlying the first-named electrical means and being electrically insulated from the first-named electrical means.

40. The device of Claim 39 wherein the laminate structure includes a third lamina of a nonconductive material disposed between the first-named and additional electrical means.

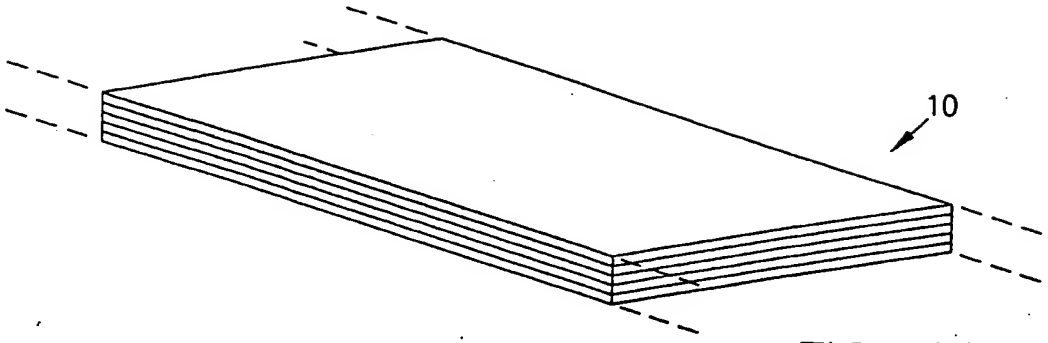


FIG. 1A

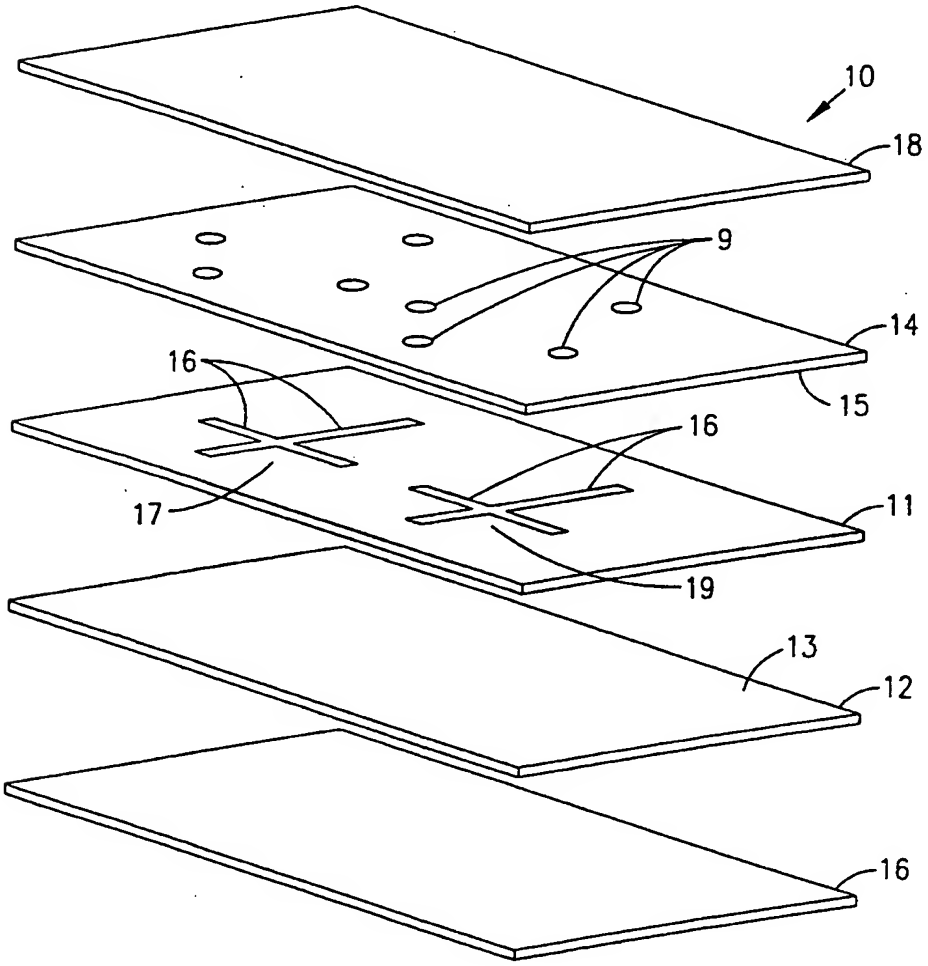


FIG. 1B

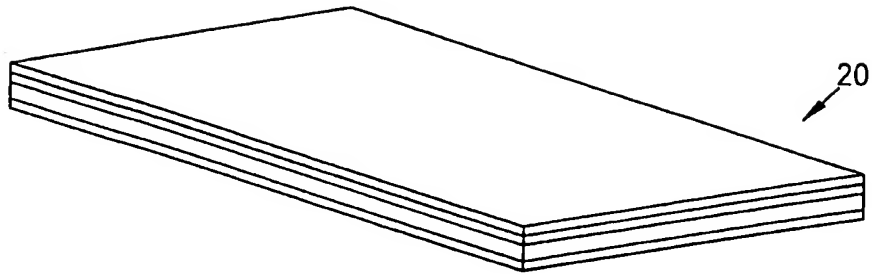


FIG. 2A

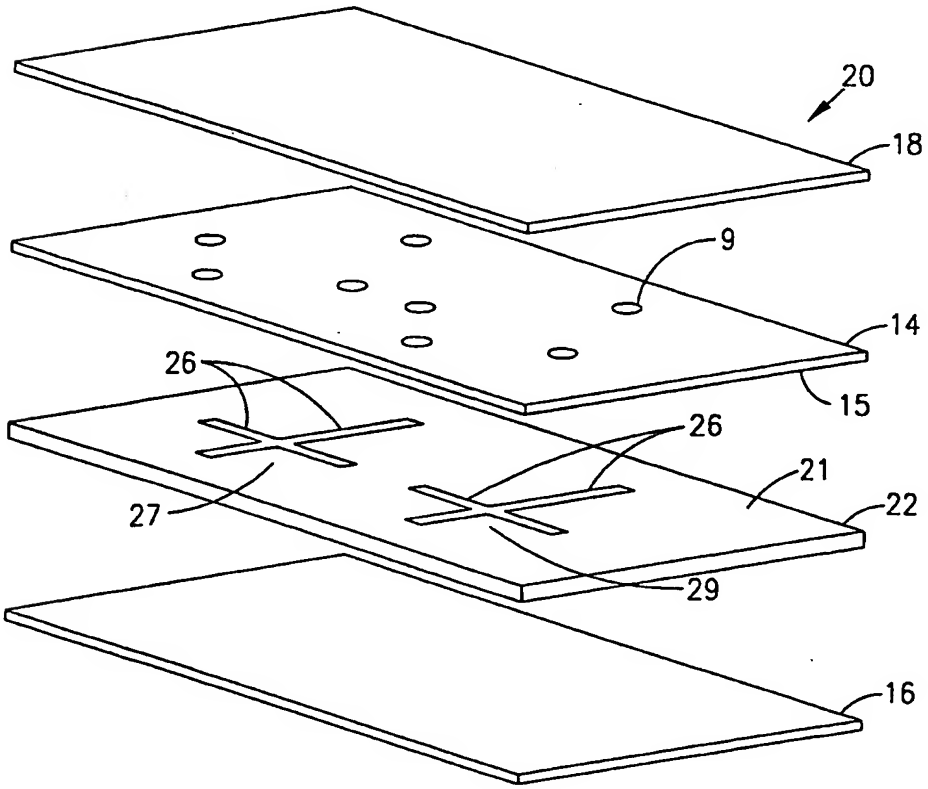


FIG. 2B